From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220 1234WO00PD01

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/052172	15.09.2004	16.09.2003

International Patent Classification (IPC) or both national classification and IPC
A61K31/58, A61K9/72, A61P11/00, A61P11/06

Applicant
ALTANA PHARMA AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☐ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-21 (with regard to industrial applicability)

because:

☒ the said international application, or the said claims Nos. 1-21 (with regard to industrial applicability) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-42
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-42
Industrial applicability (IA)	Yes:	Claims	22-42
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

SECTION III

1. Claims 1-21 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

SECTION V

2. *References*:

D1: DENT G: "CICLESONIDE" CURRENT OPINION IN INVESTIGATIONAL DRUGS, PHARMAPRESS, US, vol. 3, no. 1, 2002, pages 78-83, ISSN: 1472-4472.

D2: MEALY N E ET AL: "Ciclesonide: Treatment of allergic rhinitis antiallergy/antiasthmatic" DRUGS OF THE FUTURE, vol. 26, no. 11, November 2001 (2001-11), pages 1033-1039, ISSN: 0377-8282.

D3: US-A-5 891 844

D4: ROGERS D F: "Pulmonary mucus: Pediatric perspective" PEDIATRIC PULMONOLOGY 01 SEP 2003 UNITED STATES, vol. 36, no. 3, 1 September 2003 (2003-09-01), pages 178-188, ISSN: 8755-6863

D5: US 2003/087848 A1

D6: WO 02/04420 A

D7: WO 98/52542 A

3. *Novelty* **(Art. 33(2) PCT)**

None of the cited documents discloses the usefulness of ciclesonide for treating or preventing a respiratory disease in a patient which patient is a *child*, wherein the dose of the composition comprises ciclesonide in an amount of from 20 to 200 µg.

4. *Inventive Step* **(Art. 33(3) PCT)**

4.1 **D1** discloses the effectiveness of ciclesonide in the treatment of various respiratory diseases, for instance asthma and COPD.
Administration of 200 µg is disclosed.
Furthermore, it is reported that 'side effects, which [...] include [...] juvenile growth retardation, are dose-related and seldom occur at doses below 400 µg/day in children or 1000 µg/day in adults (beclomethasone or budesonide). An adequate asthma control can usually be maintained at lower doses than these [....]' (p. 80, right-hand col., paragraph 4).

D2 reports on ciclesonide as a very promising steroid for the treatment of asthma and allergic rhinitis with minimal systemic adverse effects - it is mentioned that steroids have been suggested to have an adverse effect on growth.
Dosages of 50 µg are disclosed.

D3 discloses compositions for the treatment of ***infant*** and acute respiratory distress syndrome containing a glucocorticosteroid, e.g. *ciclesonide* and a lung surfactant.

D4 discloses that '*inhaled corticosteroids are highly effective in the clinical management of asthma in children*'. Ciclesonide is mentioned.

D5 relates to the use of an immunostimulatory nucleic acid in combination with an asthma / allergy medicament for the treatment of asthma and allergy, for instance ciclesonide (table 2).
[113] '*The combination of immunostimulatory nucleic acids and steroids are particularly well suited to the treatment of young subjects (e.g. children). To date, the use of steroids in children has been limited by the observation that some steroid treatments have been reportedly associated with growth retardation. Thus, according to the present invention, the immunostimulatory nucleic acids can be used in combination with growth retarding steroids, and can thereby provide a "steroid sparing effect." The combination of the two agents can result in lower required doses of steroids.*'

D6 discloses piperidine compounds that can be used for the treatment of airway diseases.
'*Treatment of asthma is also to be understood as embracing treatment of subjects, e. g. of* ***less than 4 or 5 years of age,*** *exhibiting wheezing symptoms and diagnosed or diagnosable as"wheezy infants", an established patient category of major medical*

concern and now often identified as incipient or early-phase asthmatics'. (p. 13, paragraph 3).
'*The agents are also useful as co-therapeutic agents for use in combination with other drug substances .... ciclesonide*' (p. 15, paragraph 3).

4.2 Documents **D1** to **D6** disclose that ciclesonide has reduced side effects (for instance with regard to HPA-axis function) and dose ranges that correspond to the dosages disclosed in the present application (**D1** and **D2**).
D3 to **D6** specify that ciclesonide can be used in the treatment of respiratory diseases in children.

For the skilled person, it would therefore be obvious that ciclesonide is useful in the treatment of respiratory diseases in children, using dosages which are disclosed in the prior art; determination of appropriate *dosages* and *application regimens* is furthermore a *matter of routine optimization.*

The subject-matter of claims 1-42 would therefore ***not*** involve an inventive step.

5. *Industrial Applicability* **(Art. 33(4) PCT)**

5.1 For the assessment of the present claims 1-21 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

5.2 The requirements of industrial applicability would be fulfilled for the subject-matter of claims 22-42.

SECTION VIII

6.1 **D8** (AGERTOFT L ET AL: "Lower-leg growth rate and HPA-axis function in children with asthma during treatment with inhaled ciclesonide." JOURNAL OF ALLERGY

AND CLINICAL IMMUNOLOGY, vol. 113, no. 2 Supplement, February 2004 (2004-02), page S119, & 60TH ANNUAL MEETING OF THE AMERICAN ACADEMY OF ALLERGY, ASTHMA AND IMMUNOLOGY (AAAAI); SAN FRANCISCO, CA, USA; MARCH 19-23, 2004 ISSN: 0091-6749)
was *published between the priority date and the filing date* of the present application. ***On the assumption*** that the ***priority*** of the present application has been ***validly claimed***, **D8** is presently *not considered prior art* (R. 33.1 and 64.1 PCT).

6.2 Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO2004/075896	10/09/04	27/02/04	27/02/03

WO2004/075896 (**D9**) discloses combinations comprising a corticosteroid, for instance ciclesonide, for the treatment of respiratory diseases, e.g. *wheezy infant syndrome*.
The amounts which are defined in relation to the second compound ('compound A') would appear to correspond to the dosage given in the present application.